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Acute Poisoning with Neonicotinoid Insecticide

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Additional information is available at the end of the chapter

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Abstract

Neonicotinoids are a class of insecticides considered less toxic to humans than organophosphates, carbamates, organochloride and pyrethroids. The purpose of this chapter was to systematize existing data in the literature on acute intoxication with neonicotinoids to help practitioners. Clinical manifestations vary across different human systems. Gastrointestinal symptoms consist of nausea, vomiting, abdominal pain and corrosive lesions. In the central nervous system, headaches, agitation, confusion, fasciculations, seizures or coma may occur, while tachycardia or bradycardia, hypertension, hypotension and palpitations occur in the cardiovascular system. Respiratory effects are dyspnea, aspiration pneumonia or respiratory failure. Solvents that drive the insecticide also have an important role in the toxic effects. There are no specific biological tests of neonicotinoid intoxication, and their dosing is not routinely available. Treatment is symptomatic. Mortality is less than 3%, well below the poisoning with anticholinesterase insecticides, like organophosphates and carbamates.

Keywords: neonicotinoids, insecticides, poisoning, cardiovascular symptoms

1. Introduction

Poisoning with insecticides is a public health problem in many countries [1]. Organophosphates and carbamates are the principal cause of serious poisonings, sometimes leading to death. Due to the high toxicity of these compounds, new insecticides called neonicotinoids (synthetic analogs of nicotine) have been created [2].

The term “neonicotinoid” was initially used by Izuru Yamamoto for imidacloprid and related insecticides to differentiate the new insecticidal active compounds of n-AChRs from older nicotine insecticides [3].

Neonicotinoids are used in agriculture, horticulture and forestry to combat various pests. They are also used to combat fleas in domestic animals, as well as against household pests. After spraying, they act by direct contact with the insects, or by ingestion, when the insects pierce or consume the vegetative parts of plants [4]. Neonicotinoids are developed and continue to be launched on the market, often in the absence of direct human toxicity data. The human toxicity of these insecticides is often extrapolated from studies on animals, whose relevance is unclear. Therefore, more studies on acute intoxications with this class of insecticides are needed. The information resulting from these studies can contribute to the risk assessment and management of patients with neonicotinoid intoxications and support the decisions of the regulatory agencies for these substances [5]. The insecticidal activity of neonicotinoids results mainly from the agonist effect on the insects' postsynaptic nicotinic receptors for acetylcholine. They are attached to the nicotinic receptors of the postsynaptic membranes from both nerve and muscle cells and thus disrupt the transmission of the nervous influx into the central and peripheral nervous system. Additionally, this interaction with the nicotinic receptors determines their desensitization, leading to a loss of synaptic transmission of the nervous impulse [6, 7]. In recent years, some studies have suggested that neonicotinoids have a negative impact on bees near crops exposed to neonicotinoids. It is known that exposure to thiamethoxam may cause bees to be disoriented [8, 9]. In 2013, the European Food Safety Agency published a report confirming that neonicotinoids pose a risk to bees and pollinators. For this reason, under the precautionary principle, the European Commission has decided to temporarily suspend the use of three neonicotinoid substances (imidacloprid, clothianidin and thiamethoxam) for seed treatment in the agriculture of all EU member States [10]. However, in some countries, based on derogations from the ministry, they are still used.

In a large study conducted recently in three countries in Europe (the United Kingdom, Germany and Hungary), the results were contradictory: in the United Kingdom and Hungary, neonicotinoids had a negative impact on bees, while in Germany they did not seem to have affected their health status [11]. The findings of another recent Canadian study, conducted in Ontario and Quebec, are that neonicotinoids have negative effects on bees, including a 23% decrease in their life span [12]. It is therefore necessary to continue the studies on this subject in order to reach a clear and definitive scientific conclusion. Neonicotinoid insecticides are considered to have low toxicity in humans because they interact much less with nicotinic receptors in vertebrates than in insects and penetrate less the blood-brain barrier. Provided that they are less toxic in humans, neonicotinoid insecticides have become increasingly used throughout the world. However, the ingestion of large amounts of these insecticides has been associated with the occurrence of severe poisoning [13].

Hence, this review was performed in order to clarify some aspects of the diagnosis and treatment of poisonings with neonicotinoids, useful for practitioners who face such cases and maybe helping improve management of these intoxications. The physicochemical properties, toxicokinetics, experimental data and mechanism of action of neonicotinoids, clinical symptoms, diagnosis, treatment and prognosis of acute intoxication with this relatively new class of insecticides are discussed below.

2. Physicochemical properties of neonicotinoids

Neonicotinoids are classified by the EPA as both Class II and Class III agents and are labeled with the signal word “Warning” or “Caution.” Imidacloprid, the first neonicotinoid insecticide discovered in 1994 in Japan, is a structural analogue of nicotine derived from N-nitroguanidine

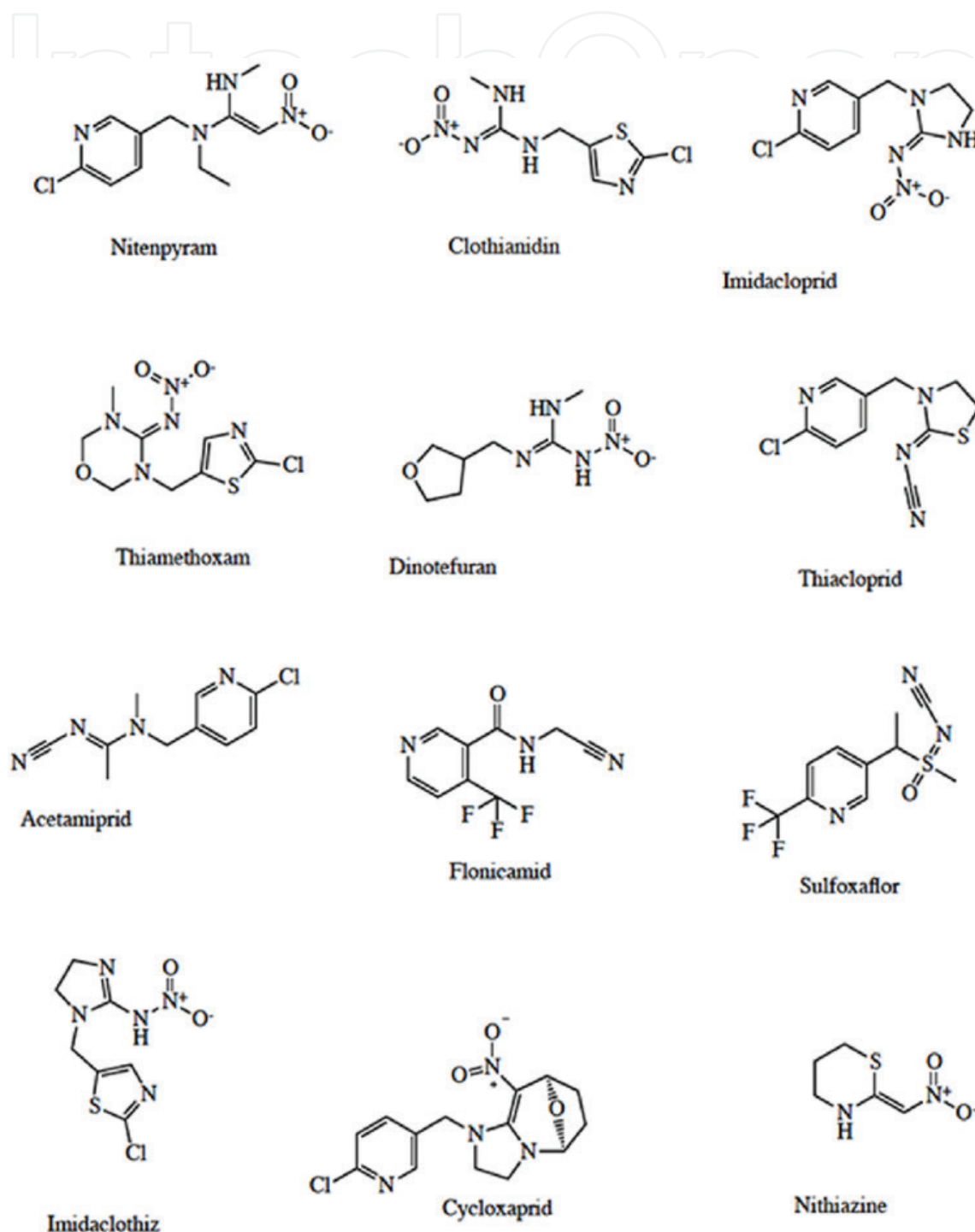


Figure 1. Common names and molecular structures of the neonicotinoids [14].

Generation of neonicotinoids	Type of neonicotinoid	Physical state
First-generation neonicotinoids	Imidacloprid	Clear crystals or beige powder
	Nitenpyram	Pale yellow crystals
	Acetamiprid	White crystals, white fine powder, odorless
	Thiacloprid	Yellow crystalline powder, odorless
Second-generation neonicotinoids	Thiamethoxam	Slightly creamy crystalline powder, odorless
	Clothianidin	Clear colorless solid powder, odorless
Third-generation neonicotinoids	Dinotefuran	White crystalline solid, odorless
	Sulfoxaflor	White solid
	Cycloxaprid	Wettable powder

Table 1. The physical state of neonicotinoids.

and is the best sold worldwide. Currently, besides imidacloprid, the neonicotinoid family includes thiamethoxam, clothianidin, thiacloprid, acetamiprid, dinotefuran, nitenpyram, niti-
azine, imidaclothiz, flonicamid, sulfoxaflor and cycloxaprid, the chemical structure of which
is shown in **Figure 1** [14]. Currently, neonicotinoids are homologated in agriculture in more
than 120 countries, being sold under various commercial names [14] (**Table 1**).

3. Toxicokinetics

Most human toxicity data available are about imidacloprid. Penetration through the skin (pre-
dominantly in the agricultural environment) of neonicotinoid insecticides is not quantified in
humans. Intoxication through the respiratory tract is negligible given that these molecules are
nonvolatile. However, there may be a secondary swallowing of the inhaled aerosol micropar-
ticles. The first prospective study conducted in Sri Lanka by Mohamed F. et al. on 68 patients
(61 with voluntary ingestion and 7 with cutaneous exposure) showed that the mean plasma
concentration of imidacloprid was 10.58 ng/l, IQR: 3.84–15.58 ng/l, range: 0.02–51.25 ng/l. In
seven patients, the plasma concentration remained elevated for 10–15 h postingestion, sug-
gesting that absorption and/or elimination may be prolonged at high doses. The time-concen-
tration profiles have demonstrated a rapid initial absorption [5]. The plasma peak is reached
within 2 h. There is no preferential distribution in fat-rich tissues [15]. In insects, mammals
and plants, neonicotinoids undergo phase I and phase II biotransformation (**Figure 2**).

In vitro studies on the metabolism of neonicotinoids have indicated the importance of cyto-
chrome P450s (CYP) in their oxidation and reduction. Through a variety of human CYP iso-
enzymes, imidacloprid is oxidized to 5-hydroxyimidacloprid and imidacloprid olefin and
reduced to nitrosoguanidine, aminoguanidine and urea imidacloprid. The most active CYP
isoenzyme for oxidation of the imidacloprid residue is CYP 3A4 (CYP most abundant in
humans), followed by CYP 2C19, 2A6 and 2C9. For nitroreduction, the most active CYP are:
CYP 1A2, 2B6, 2D6 and 2E1 [16, 17].

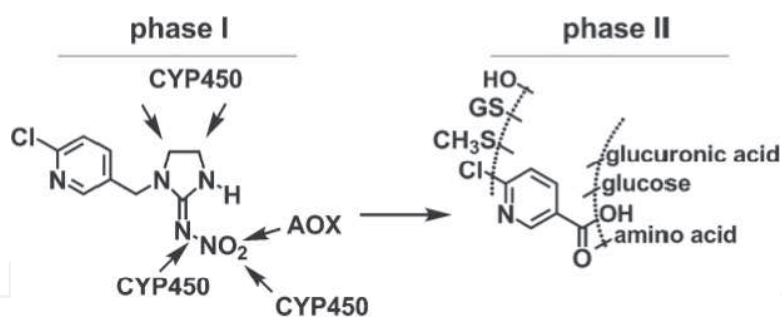


Figure 2. Sites of metabolite attack on IMI and 6-chloronicotinic acid (CNA) for phase I and phase II reactions [16].

Thiamethoxam is converted to clothianidin, which is more active than the parent molecule, mostly by CYP 3A4 and to a lesser extent by CYP 2C19 and 2B6, and is demethylated by 2C19. Clothianidin is demethylated by CYP 3A4, 2C19 and 2A6 [18]. There is no accumulation of neonicotinoids in the body: over 90% are eliminated in less than 24 h and totally in 48 h [15, 19].

4. Experimental data and mechanisms of action

Neonicotinoids are neither irritating to eyes and skin (rabbit) nor sensitizing (guinea pigs) [15]. Their acute toxicity to mammals is variable depending on the type of neonicotinoid. The amount of toxic product that kills 50% of the experimental animals, called the lethal dose (LD 50), is illustrated in **Table 2** for the main neonicotinoids.

With an LD 50 of 425–475 mg/kg administered orally in rats, the toxicity of imidacloprid is mild to moderate. A single 42 mg/kg dose has no effect. After 2–6 h, poisoned animals present with apathy, trembling with ataxia, hypothermia and respiratory arrest [19, 20].

Neonicotinoids have been designed to be effective as insecticides by contact or ingestion [21]. In both insects and humans, neonicotinoids behave as postsynaptic acetylcholine receptor agonists, which are neurotransmitters of the central nervous system, the parasympathetic nervous system and some of the sympathetic system. Their irreversible linkages with these receptors initially stimulate, then rapidly block the Na^+/K^+ channels and inhibit the transmission of the nervous influx. Their high insect toxicity is explained by the predominance of nicotinic receptors in the central nervous system of these species, by

Common name	Local effects	Rat oral LD50	Rabbit dermal LD50
Acetamiprid	Absent	450	>2000
Clothianidin	Absent	>5000	>2000
Dinotefuran	Absent	2000	>2000
Imidacloprid	Absent	4870	>2000
Thiamethoxam	Absent	>5000	>2000

Table 2. Neonicotinoid pesticides mammalian toxicities (mg/kg of body weight) [7].

the absence of the blood-brain barrier and by their affinity for some insect-specific receptor subtypes, in particular $\alpha 4\beta 2$ [19]. In mammals, the predominant receptor subtype is $\alpha 4\beta 2$, which is found to have the highest density in the thalamus. In the developing brain, this subtype is involved in proliferation, apoptosis, migration, differentiation, synapse formation and neuronal circuits [22]. Given that in mammals nicotinic receptors have a wider distribution (neuromuscular junction), the neonicotinoid affinity for these receptors is lower and the central action is reduced because of poor intracerebral penetration [17]. The toxicity of imidacloprid is very low in dermal exposure and is moderate in case of ingestion. In case of inhalation, the toxicity is variable: as dust it is considered to be slightly toxic, but as aerosols it is very toxic [23].

5. Epidemiology of acute poisoning with neonicotinoids in humans

Despite the widespread use of neonicotinoids, there are few reports in the literature on human toxicity. The first case report was made in 2001 by Wu IW et al. Clinical manifestation included drowsiness, disorientation, dizziness, oral and gastroesophageal erosions, hemorrhagic gastritis, productive cough, fever, leukocytosis and hyperglycemia. The patient recovered without complications with supportive treatment and was discharged 4 days after ingestion [24]. Most cases were reported in USA (Texas), France, China and Sri Lanka [25, 26, 13]. The epidemiological aspects resulting from these studies are summarized in **Table 3**.

Studies	Cohort of the study	Country of study	Epidemiological findings
Forrester M et al., 2014 [25]	1142 cases of acute intoxication reported by Texas Intoxication Control Centers over the period 2000–2012 (retrospective study)	USA	<ul style="list-style-type: none">• 77% with imidacloprid• 17% with dinotefuran• 64% female• 32 serious cases (2.9%)• Intoxication mode: ingestion (51%), cutaneous (44%) and ocular (11%)• 28% children aged <5 years and 9% aged 6–19 years• 97% accidental
Boels D, Chataigner D, 2014 [26]	482 cases of acute poisoning with imidacloprid between January 1999 and December 2012 (retrospective study)	France	<ul style="list-style-type: none">• Increase from 8 cases in 1999 to 34 cases in 2012• 120 cases (28%) were children <5 years• 37 cases (8.6%) children aged 5–14 years• 389 poisonings were accidental, 24 voluntary, and in 15 cases it was not possible to specify the circumstances of intoxication• Seven cases were serious, requiring intensive care

Studies	Cohort of the study	Country of study	Epidemiological findings
Phua DH et al, 2009 [13]	70 cases of acute intoxication reported by the Taiwan National Poison Center between 1987 and 2007 (retrospective study)	China	<ul style="list-style-type: none"> • Dramatic increase in the number of cases between 2003 and 2007: 58 cases out of the total of 70 • Two children with accidental poisoning • 67 males • 48 cases were suicidal attempts, of which eight consumed ethanol • Toxic: imidacloprid (64 cases), acetamiprid (4) and clothianidin (2). • Two deaths (mortality rate 2.9%)
Mohamed F et al., 2009 [5]	68 cases of acute poisoning with imidacloprid between March 2002 and March 2007 (prospective study)	Sri Lanka The dosing was done in laboratories in Australia	<ul style="list-style-type: none"> • 61 out of 68 patients (91%) were intoxicated by ingestion • 82% were voluntary poisonings

Table 3. The main epidemiological aspects of neonicotinoid intoxication studies.

The prevalence of voluntary intoxication was different from one study to another: only 2% in the study in Texas and 4.9% in the study in France, as opposed to the studies in China and Sri Lanka, where 81% and 82%, respectively, were classified as an attempt of suicide [25, 26, 13].

There are also differences in childhood poisoning frequency: in the study conducted in Texas, 37% were patients under the age of 19, and in France 36.6% were children under the age of 14, whereas the study in China recorded only two children with accidental poisoning. The study in Sri Lanka does not specify the age of the patients.

Regarding the manner of intoxication, in the US study only 51% of poisoning occurred through ingestion, compared to 91% (61/68 cases) in Sri Lanka and 81% (57/70) in China.

In addition to these studies, several sporadic cases have been reported. Thus, eight cases were reported in India [27–33], two in Turkey [34, 35], two in Portugal [36], two in Colombia [37], two in Japan [38], one case in Saudi Arabia [39], Iran [40], Poland [41] and four cases in Taiwan [41–45].

6. Clinical symptoms of poisoning by neonicotinoids

Symptoms of neonicotinoid poisoning appear to be less severe in humans than in insects, because their affinity for human nicotinic receptors is lower and they do not cross the blood-brain barrier. Clinical picture is better known for intoxication with imidacloprid, which is the oldest neonicotinoid used as an insecticide. A large study conducted in Texas between 2000 and 2012 on 1142 patients with neonicotinoid exposure found that the main symptoms are: eye irritation and dermatitis, nausea, vomiting, corrosive oral mucosal lesions,

Symptomatology	Benign forms Minor, mild symptoms that spontaneously regress	Moderate forms Pronounced or prolonged symptoms or signs	Severe forms Severe symptoms that threaten vital prognosis
Neurological	<ul style="list-style-type: none"> • Sleepiness, vertigo, ataxia, tinnitus • Glasgow score 12–14 • Slight agitation • Minor extrapyramidal symptoms • Minor cholinergic/anticholinergic symptoms • Paresthesia • Minor visual and hearing impairments 	<ul style="list-style-type: none"> • Disturbances of consciousness with delayed response to pain • Glasgow score 8–11 • Apnea, bradypnea • Confusion, agitation, hallucinations, delirium • Localized or generalized seizures (rarely) • Marked extrapyramidal symptoms • Noticeable cholinergic/anticholinergic symptoms • Isolated paralysis without affecting vital functions • Visual and auditory disturbances 	<ul style="list-style-type: none"> • Deep coma with inappropriate or absent response to pain • Glasgow score 3–7 • Depression or respiratory failure • Extreme agitation • Generalized seizures • Convulsive state, opisthotonus • Generalized paralysis or paralysis that affects vital functions • Blindness, deafness
Eye	<ul style="list-style-type: none"> • Irritation, conjunctival hyperemia, tears • Minor eyelid edema 	<ul style="list-style-type: none"> • Marked irritation • Limited, circumscribed corneal involvement • Punctual keratitis 	<ul style="list-style-type: none"> • Corneal ulcer • Corneal perforations • Definitive sequelae
Skin	<ul style="list-style-type: none"> • Irritation, first-degree burns • Second-degree burns and <10% body surface area (BSA) 	<ul style="list-style-type: none"> • Second-degree burns with 10–50% BSA to adult and 10–30% BSA to child • Third-degree marks <2% BSA 	<ul style="list-style-type: none"> • Second-degree burns >50% BSA to adult and >30% BSA to child • Third-degree burns >2% BSA
Bites/stinging	<ul style="list-style-type: none"> • Edema, localized pruritus • Discrete pain 	<ul style="list-style-type: none"> • Localized edema involving the entire member • Localized necrosis • Moderate pain 	<ul style="list-style-type: none"> • Extensive edema comprising the adjacent member and the adjacent parts • Critical location of edema with danger to the integrity of the upper airways

Symptomatology	Benign forms Minor, mild symptoms that spontaneously regress	Moderate forms Pronounced or prolonged symptoms or signs	Severe forms Severe symptoms that threaten vital prognosis
Muscle	<ul style="list-style-type: none"> Slight or moderate pain Sensitivity to palpation Rhabdomyolysis CPK: 250–1500 ui/l 	<ul style="list-style-type: none"> Pain, stiffness, cramps Fasciculations Rhabdomyolysis CPK: 1500–10,000 ui/l 	<ul style="list-style-type: none"> Intense pain, extreme rigidity Extensive cramps Extended, diffuse fasciculations Rhabdomyolysis with complications CPK > 10,000 ui/l Compartment syndrome
Kidney	<ul style="list-style-type: none"> Proteinuria and/or minimal hematuria 	<ul style="list-style-type: none"> Proteinuria and/or massive hematuria Oliguria, polyuria Serum creatinine: 200–500 mmol/l 	<ul style="list-style-type: none"> Kidney failure, anuria Serum creatinine >500 µmol/l
Blood	<ul style="list-style-type: none"> Minor hemolysis Methemoglobinemia ranging from 10 to 30% 	<ul style="list-style-type: none"> Hemolysis Methemoglobinemia ranging from 30 to 50% Coagulation disorders without bleeding Anemia, leukopenia, thrombocytopenia 	<ul style="list-style-type: none"> Massive hemolysis Methemoglobinemia >50% Coagulation disorders with bleeding Anemia, leukopenia, severe thrombocytopenia
Liver	<ul style="list-style-type: none"> ASAT, ALT: 2–5 times normal 	<ul style="list-style-type: none"> ASAT, ALAT: 5–50 times normal Without obvious clinical signs of liver dysfunction 	<ul style="list-style-type: none"> ASAT, ALT >50 times normal Affecting clotting factors Clinical signs of liver failure

Table 4. The symptomatology of imidacloprid poisoning depending on severity [26].

dizziness, hypertension and tachycardia [25]. The French Toxicity Co-ordination Committee analyzed 428 cases of exposure to imidacloprid between 1999 and 2012, of which over 27% were children under 5 years of age. As a result of this study, the symptomatology was better outlined according to the severity of the intoxication (mild, moderate or severe), as illustrated in **Table 4** [26].

There was reported a case with concomitant intoxication with imidacloprid and alcohol ingestion, resulting in multiple organ failure [45]. Another case was reported by Agarwal and Srinivas, manifesting severe neuropsychiatric disorders and rhabdomyolysis [31]. In Colombia, Estrada et al. signaled two cases admitted with digestive manifestations, coma (Glasgow score 6 and 3, respectively) and respiratory failure with 70–75% Sa O₂. One of the patients also presented dormant miosis and was thus given atropine [37]. In Saudi Arabia, there was a case with generalized erythematous maculopapular rash typical of leukoclastic vasculitis, which was confirmed by biopsy. It also associated hepatic and renal dysfunction, requiring dialysis [40]. Another case reported in Taiwan presented fatal ventricular fibrillation [45].

The main symptoms of acetamiprid poisoning are severe nausea, vomiting, muscle weakness, hypothermia and convulsions [46]. Clinical manifestations include tachycardia, hypotension, electrocardiogram changes, hypoxia and thirst in the case of the highest serum concentration of acetamiprid. The symptoms were partly similar to acute organophosphate intoxication [30]. In one case, ventricular fibrillation that lasted 11 h after ingestion was described [45]. Similar to imidacloprid poisonings, there was reported a case of severe multiple organic dysfunction [43]. Another case of acetamiprid intoxication was by suicidal ingestion, where symptoms included prolonged muscle weakness, similar to the intermediate syndrome in organophosphorus intoxication. The case resolved in about 3 weeks [35].

Symptoms of thiamethoxam intoxication are less known, and cases are rarely reported. Vinod et al. noted a case manifesting nausea, vomiting, agitation and multiple episodes of generalized tonic-clonic seizures within the first 2 h of ingestion of thiamethoxam. Subsequently, coma, hypotension, renal failure, metabolic acidosis and rhabdomyolysis occurred, with fatal outcome 36 h after ingestion [29].

Solvents used in neonicotinoid insecticide solutions can also play an important part in poisoning symptoms. Although not all solvents contained by neonicotinoid insecticides are known, most of them use N-methylpyrrolidone. Ingestion of a large amount of this substance irritates the upper gastrointestinal tract and causes oral ulceration, nausea, vomiting, dysphagia, odynophagia and abdominal pain [24].

7. Diagnosis of poisoning incidents

The diagnosis is based on anamnesis and clinical symptoms. There are no specific abnormalities of acute poisoning with neonicotinoids [5]. There may be metabolic disturbances (**Table 5**). Dosage of neonicotinoids is not routinely available, its interest being purely medicolegal. Depending on the symptomatology of each case, additional investigations may be necessary.

Clinical forms	Mild	Moderate	Severe
Acidobasic disorders	<ul style="list-style-type: none"> • HCO_3^-: 15–20 or 30–40 mmol/l • pH: 7.25–7.32 or 7.50–7.59 	<ul style="list-style-type: none"> • HCO_3^-: 10–14 sau > 40 mmol/l • pH: 7.16–7.24 sau 7.60–7.69 	<ul style="list-style-type: none"> • $\text{HCO}_3^- < 10$ mmol/l • pH < 7.15 or > 7.7
Electrolytic disorders	<ul style="list-style-type: none"> • K: 3–3.4 or 5.2–5.9 mmol/l • Moderate hypoglycemia: 0.5–0.7 g/l or 2.8–3.9 mmol/l • Short-term hyperthermia 	<ul style="list-style-type: none"> • K: 2.5–2.9 or 6–6.9 mmol/l • Severe hypoglycemia: 0.3–0.5 g/l or 1.7–2.8 mmol/l • Prolonged hyperthermia 	<ul style="list-style-type: none"> • K: < 2.5 or > 7 mmol/l • Severe hypoglycemia < 0.3 g/l or < 1.7 mmol/l • Malignant hyperthermia/hypothermia

Table 5. Metabolic disorders depending on the severity of intoxication [26].

Depending on the intensity and duration of cardiovascular, respiratory and digestive symptoms, three degrees of severity can be distinguished (**Table 6**):

1. Benign: mild symptoms that spontaneously regress;
2. Moderate: pronounced or prolonged symptoms/signs;
3. Severe: severe symptoms that may influence the vital prognosis.

Forms	Cardiovascular symptoms	Respiratory symptoms	Digestive symptoms
Benign	<ul style="list-style-type: none"> • Isolated extrasystoles • Discrete, transient hypotension • Transient, discrete hypertension 	<ul style="list-style-type: none"> • Airways irritation • Coughing, breathlessness • Slight dyspnea • Slight bronchospasm • Abnormal thoracic radiography with or without minor symptoms 	<ul style="list-style-type: none"> • Vomiting • Diarrhea • Abdominal pain • Minor oral ulceration • Endoscopy: erythema, stage I edema
Moderate	<ul style="list-style-type: none"> • Sinus bradycardia: <ul style="list-style-type: none"> ○ Adults 40–50 b/min ○ Children 60–80 b/min ○ New born 80–90 b/min • Frequent premature beats • Atrial flutter/fibrillation • AVB grade I or II • Prolonged QRS and QTc • Repolarization modifications • Myocardial ischemia • Hypo/hypertension 	<ul style="list-style-type: none"> • Prolonged cough • Stridor, bronchospasm • Dyspnea • Hypoxia requiring oxygen administration • Abnormal pulmonary radiography with moderate symptoms 	<ul style="list-style-type: none"> • Pronounced or prolonged vomiting • Diarrhea • Abdominal pain • First-grade burns of a critical area or II and III grade burns on limited areas • Dysphagia • Endoscopy: stage IIa transient ulcerative lesions

Forms	Cardiovascular symptoms	Respiratory symptoms	Digestive symptoms
Severe	<ul style="list-style-type: none">• Severe sinus bradycardia:<ul style="list-style-type: none">◦ Adults <40 b/min◦ Children <60 b/min◦ New born <80 b/min• Severe sinus tachycardia<ul style="list-style-type: none">◦ Adults >180 b/min◦ Children >190 b/min◦ New born >200 b/min• Ventricular dysrhythmia with vital prognosis• AVB grade III• Asystole• Myocardial infarction• Shock• Malignant hypertensive disorder	<ul style="list-style-type: none">• Respiratory failure: severe bronchospasm, dyspnea, airway obstruction, ARDS, pulmonary edema, glottis edema, bronchopneumonia, pneumopathy, pneumothorax• Abnormal pulmonary radiography with severe symptoms	<ul style="list-style-type: none">• Severe digestive hemorrhage• Digestive perforation• Enlarged II and III grade burns• Severe dysphagia• Endoscopy: transmural ulcer lesions, circumferential lesions, perforations stage IIB, III and IV

Table 6. Degrees of severity according to intensity and duration of cardiovascular, respiratory and digestive symptoms [26].

Differential diagnosis should take into account intoxications with other pesticides. This poisonings can mimic light forms of organophosphorus or carbamates intoxications. Also, many cases reported involved combinations of multiple pesticides and ethanol [5, 13].

8. Management of poisoning incidents

Management of acute neonicotinoid insecticide poisoning is mainly symptomatic and supportive. Dermal and mucosal exposures should be decontaminated as soon as possible [13].

In case of coma and respiratory distress, intubation and assisted ventilation associated with hemodynamic support are required. The presence of solvents in liquid neonicotinoid formulas makes the activated charcoal and gastric lavage or vomiting ineffective, due to the risk of inhalation pneumonia [13]. Gastric lavage and activated charcoal should be avoided if corrosive injuries of the oral and gastrointestinal mucosa are found. Activated charcoal may hinder endoscopic evaluation of patients with corrosive lesions [13]. Prudent aspiration of the gastric contents can be considered, with respiratory protection, and if the ingested volume is high (over 100 ml), the ingestion period is short (less than 1 h) [13, 15]. The respiratory effects of neonicotinoids should be carefully monitored, particularly hypoventilation and respiratory failure. Patients with upper airway injuries such as hoarseness and stridor caused by irritant and corrosive effects of the solvent should probably undergo endoscopic assessment of vocal cordons [13].

Sometimes, organophosphorus intoxication may also be associated. In this case, acute poisoning may be manifested by miosis, bradycardia, hypersalivation and bronchorrhea. Because of these symptoms, atropine and oximes may be improperly used as an antidote. It is unknown whether these drugs are effective or may worsen the outcome of neonicotinoid insecticide poisonings. In cases with life-threatening muscarinic manifestations (e.g., bronchorrhea with airway compromise), the use of atropine may be justified in neonicotinoid-poisoned patients [13, 44]. Oximes (e.g., pralidoxime) are usually either ineffective or contraindicated. In the absence of organophosphorus pesticides, oximes have a weak inhibitory effect on acetylcholinesterase activity and therefore may increase nicotinic effects (tachycardia, hypertension and muscle weakness) [5]. Because the severity of poisoning is not proportional to the plasma concentration of neonicotinoids, hemofiltration is ineffective in increasing their elimination [13, 43].

9. Prognosis and comparative mortality rates

The numbers of neonicotinoid poisonings have increased in the last decade, given that neonicotinoid insecticide is highly used. Respiratory, cardiovascular and certain neurological presentations (dyspnea/apnea, coma, tachycardia, hypotension, mydriasis and bradycardia) are symptoms of severe neonicotinoid intoxication [43]. Biochemical abnormalities and rhabdomyolysis have been reported as potentially serious complications that might lead to mortality [5].

Mortality through imidacloprid poisoning ranges from 0% to 4.2% in various studies. In a study in Taiwan, neonicotinoid poisoning mortality was 2.9%, inferior to that with organophosphates (12.3%) or carbamates (7.3%), but close to that with synthetic pyrethroids (3.1%) [47]. In the study in France conducted on 428 patients with acute neonicotinoid poisoning, six deaths were recorded [26]. Another study in Korea on 24 cases shows a mortality rate of 4.2% [48]. In addition to these studies on larger cohorts of patients, sporadic cases of acute neonicotinoid poisoning deaths are also reported in the literature (Table 7).

Authors, year of the study	Place of study	The type of neonicotinoid	Death numbers
Proença P et al., 2005 [36]	Portugal	Imidacloprid	2
Huang NC et al., 2006 [45]	Taiwan	Imidacloprid	1
Shadnia S et al., 2008 [40]	Iran	Imidacloprid	1
Yeh IJ et al., 2010 [44]	China	Imidacloprid	1
Iyyodurai R et al., 2010 [30]	India	Imidacloprid	1
Harish J et al., 2011 [49]	India	Imidacloprid	1
Fuke C et al., 2014 [49]	Japan	Imidacloprid	1
Vinod KV et al., 2015 [29]	India	Thiacloprid	1

Table 7. Deaths by acute poisoning with neonicotinoids reported in the literature.

10. Concluding remarks

Neonicotinoids act quite selectively on insects, but they are not free of human toxicity. Several cases of acute intoxication with such insecticides, sometimes severe, resulting in death, have been reported in the literature. The above review has highlighted the consequences of poisoning with these newer pesticides, not very well known at the moment. Therefore such information is valuable for clinicians, regulatory authorities and the public at large. Given the fact that these insecticides are increasingly being used in agriculture, horticulture and fish farming, but also for combating domestic pests, more studies on the human health effects of neonicotinoids exposure are needed and maybe some awareness programs about its toxicity should be implemented.

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